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(57) Abstract

The present invention provides a method for identifying a binding molecule having selective affinity for a ligand. The method consists of selectively immobilizing a diverse population of binding molecules to a solid support, simultaneously contacting the diverse population immobilized on the solid support with two or more ligands and determining at least one binding molecule which selectively binds to one or more of the ligands. The invention additionally provides a method for identifying an antibody having selective affinity for a tumor antigen. The method consists of selectively immobilizing a diverse population of antibodies to a solid support, simultaneously contacting the diverse population immobilized on the solid support with two or more tumor antigens and determining at least one antibody which selectively binds to one or more of the tumor antigens. The invention also provides an isolated binding polypeptide selective for a tumor antigen. Further provided by the present invention is a Complementarity Determining Region (CDR) or functional fragment thereof of an antibody selective for a tumor antigen.

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METHODS FOR IDENTIFYING LIGAND SPECIFIC BINDING MOLECULES

This application claims the benefit of priority of United States Serial No. 08/905,825, filed August 4, 1997, which was converted to a United States Provisional Application, the entire contents of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates generally to tumor cell therapy and more specifically to methods of identifying new tumor specific binding molecules and tumor specific antigens.

Recent years have provided tremendous progress in the understanding of cancer development and progression. Despite this increased knowledge, only marginal decreases in death rates from most types of cancer have been observed. The success rate of cancer therapy is increased with early diagnosis. Cancer therapy generally involves treatment with therapeutic agents that affect not only cancer cells but other cells in the body as well, often leading to debilitating side effects. Thus, identification of tumor-specific targeting agents, such as antibodies that bind to tumor antigens, would provide reagents useful for earlier diagnosis of specific types of cancers as well as tumor-specific targeting agents for cancer therapy that minimizes impact on non-tumor tissues.

Although some tumor-specific antigens have been identified, obtaining useful tumor-specific targeting agents has remained elusive. Of interest for therapeutic purposes are human antibodies that can be used to target toxins to specific types of tumors. The advantage of using human antibodies is that they are least likely to

cause an immune response that would remove the antibody and toxin from the body during cancer therapy. However, development of human antibodies capable of targeting specific tumors has proven difficult.

To obtain antibodies or other agents capable of specifically targeting tumor types, a screen of a large number of possible agents is required. For example, to obtain a monoclonal antibody specific for a tumor antigen, it is necessary to generate and screen tens or hundreds of hybridoma cell lines. The process is laborious, time consuming and additionally requires the initial purification or preparation of the antigen or tumor cell.

A number of other screening approaches have now been developed, including recombinant methods utilizing bacteria and yeast, that allow identification of specific binding partners for a particular molecule of interest. For example, it is now possible to produce large display or combinatorial libraries of antibodies or other types of binding molecules. However, these methods generally require the screening of the libraries using one or more relatively purified molecules of interest.

Regardless of the available screening approaches, the identification of tumor specific antigens and their subsequent isolation has proven difficult over the years. Methods which have attempted to circumvent this problem through the use of cell lysates to screen for specific binding molecules has unfortunately resulted in molecules which exhibit inadequate binding specificities. Therefore, the availability of specific binding molecules which can be adapted to cancer diagnosis and therapy has been inherently lacking.

Thus, there exists a need for rapid and efficient methods to identify specific binding molecules to tumor antigens. The present invention satisfies this need and provides related advantages as well.

SUMMARY OF THE INVENTION

The present invention provides a method for identifying a binding molecule having selective affinity for a ligand. The method consists of selectively immobilizing a diverse population of binding molecules to a solid support, simultaneously contacting the diverse population immobilized on the solid support with two or more ligands and determining at least one binding molecule which selectively binds to one or more of the ligands. The invention additionally provides a method for identifying an antibody having selective affinity for a tumor antigen. The method consists of selectively immobilizing a diverse population of antibodies to a solid support, simultaneously contacting the diverse population immobilized on the solid support with two or more tumor antigens and determining at least one antibody which selectively binds to one or more of the tumor antigens. The invention also provides an isolated binding polypeptide selective for a tumor antigen. Further provided by the present invention is a Complementarity Determining Region (CDR) or functional fragment thereof of an antibody selective for a tumor antigen.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the optimization of human Fab binding molecule immobilization on a solid support.

Figure 2 shows the identification of human Fab binding molecules to tumor antigens using binding molecules selectively immobilized on a solid support and compares detection efficiencies to binding molecules directly immobilized on a solid support.

Figure 3 shows the increased binding specificity and decreased background of detection using selective immobilization of human Fab binding molecule populations on a solid support compared to direct immobilization.

Figure 4 shows the binding specificity of human Fab binding molecules identified by selective immobilization on a solid support to tumor cell monolayers.

Figure 5 shows fluorescent activated cell sorting of tumor cells with human Fab binding molecules identified by selective immobilization on a solid support.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides rapid and efficient methods for the identification of binding molecules which exhibit selective affinity for one or more ligands of interest. The methods are advantageous in that they allow the simultaneous screening of multiple binding molecules against multiple ligands of interest. Moreover, very little information is required regarding the identity or function of either the binding molecule or the ligand. For example, diverse populations of binding molecules can be simultaneously screened against diverse populations of ligands to rapidly identify

numerous molecules exhibiting a desired binding specificity. The methods of the invention can therefore be advantageously applied for the discovery of specific reagents for diagnosis and treatment of human diseases.

As used herein, the term "binding molecule" is intended to refer to a molecule of sufficient size and complexity so as to be capable of selectively binding a ligand. Such molecules are generally macromolecules, such as polypeptides, nucleic acids, carbohydrate or lipid. However, derivatives, analogues and mimetic compounds as well as small organic compounds are also intended to be included within the definition of this term. The size of a binding molecule is not important so long as the molecule exhibits or can be made to exhibit selective binding activity to a ligand. For example, a binding molecule can be as little as about one or two, and as many as tens or hundreds of monomer building blocks which constitute a macromolecule binding molecule. Similarly, an organic compound can be a simple or complex structure so long as selective binding affinity can be exhibited.

Binding molecules can include, for example, antibodies and other receptor or ligand binding polypeptides of the immune system. Such other molecules of the immune system include for example, T cell receptors (TCR), major histocompatibility complex (MHC), CD4 receptor, and CD8 receptor. Additionally, cell surface receptors such as integrins, growth factor receptors and cytokine receptors, as well as cytoplasmic receptors such as steroid hormone receptors are substantially also included within the definition of the term binding molecule. Furthermore, DNA binding polypeptides such as transcription factors and DNA

replication factors are likewise included within the definition of the term binding molecule. Finally, polypeptides, nucleic acids and chemical compounds such as those selected from random and combinational libraries are also included within the definition of the term so long as such a molecule exhibits or can be made to exhibit selective binding activity toward a ligand.

As used herein, the term "polypeptide" when used in reference to a binding molecule or a ligand is intended to refer to peptide, polypeptide or protein of two or more amino acids. The term is similarly intended to refer to derivatives, analogues and functional mimetics thereof.

As used herein, the term "ligand" refers to a molecule that can be selectively bound by a binding molecule. A ligand can be essentially any type of molecule such as polypeptide, nucleic acid, carbohydrate, lipid, or any organic derived compound. Those skilled in the art know what is meant by the meaning of the term ligand. Specific examples of ligands are the tumor antigens described herein which are selectively bound by the human antibody binding molecules described in the examples.

As used herein, the term "diverse population" is intended to refer to a group of two or more different molecules. A diverse population of binding molecules can have similar biochemical function as long as the function or structure of the binding molecules are not identical. A diverse population can include, for example, a population of binding molecules that are antibodies capable of recognizing the same or different ligands. Moreover, the same binding molecule can recognize two

different ligands based on different ligand conformations. In such cases, the binding molecules would be considered distinct based on function and multiple molecules of the same binding molecule would therefore comprise a diverse population.

As used herein, the term "selective" or "selectively" when referring to the binding of a binding molecule to a ligand or the immobilization of a population to a solid support is intended to mean that the interaction can be discriminated from unwanted or non-specific interactions. Discrimination can be based on, for example, affinity or avidity and therefore can be derived from multiple low affinity interactions or a small number of high affinity interactions. For example, a binding molecule interaction with a ligand is generally greater than about 10^{-4} M, is preferably greater than about 10^{-5} M and more preferably greater than about 10^{-6} M. High affinity interactions are generally greater than about 10^{-8} M to 10^{-9} M or greater.

As used herein, the term "immobilizing" or grammatical equivalents thereof, refers to the attachment, as through the binding of a population of binding molecules, to a solid support. Immobilization can be through specific interactions with the binding molecule and an agent on the solid support. The agent can be, for example, a chemical moiety which allows covalent or non-covalent interactions sufficient to hold the population of binding molecules to the solid support. Immobilization can also be through tethers or linkers. Such linkers can be covalent linkers, hydrolyzable linkers, photo-labile linkers or other linkers that allow the binding molecules to be selectively attached. Linkers can also be polypeptides or other biomolecular

linkers such as antibodies, lipid attachments, streptavidin, receptors, fusion polypeptides, or any biomolecule that can tether the binding molecule to the solid support. Additionally, domains of polypeptides can similarly be linkers. For example, hydrophobic domains which allow direct absorption to a plastic due to specific sequences which are molecular tags or recognition sequences can be linkers for binding polypeptides.

As used herein, the term "solid support" refers to a solid medium which is sufficiently stable so as to allow immobilization of a population of binding molecules. Solid supports can include, for example, membranes such as nitrocellulose, nylon, polyvinylidene difluoride, plastic, glass, polyacrylamide or agarose. Solid supports can also be made in essentially any size or shape so long as it supports the immobilization of a population of binding molecules. For example, the solid support can be a flat planar surface such as a natural or synthetic membrane filter or a glass slide. Alternatively, the solid support can be of various spherical shapes, including, for example, beads made of glass, polyacrylamide or agarose. Porous mediums can similarly be used as solid supports and such mediums are included within the definition of the term as used herein. Additionally, any of the solid supports can be modified, for example, to include functional chemical groups that can be used directly or indirectly for attachment of binding molecules or linkers.

As used herein, the term "antibody" refers to a polypeptide which binds to a ligand and is intended to be used consistently with its meaning within the art. The term immunoglobulin is similarly intended to fall within

What is claimed is:

1. A method for identifying a binding molecule having selective affinity for a ligand, comprising the steps of:

a) selectively immobilizing a diverse population of binding molecules to a solid support;

b) simultaneously contacting said diverse population immobilized on said solid support with two or more ligands; and

c) determining at least one binding molecule which selectively binds to one or more of said ligands.

2. The method of claim 1, further comprising determining the sequence of said binding molecule determined in step (c).

3. The method of claim 1, further comprising the step of characterizing said ligand which binds to said binding molecule.

4. The method of claim 1, wherein said population of binding molecules is produced in an expression library.

5. The method of claim 4, wherein said expression library is an antibody library.

6. The method of claim 1, wherein said ligands are polypeptides.

7. The method of claim 6, wherein said polypeptides are cell surface polypeptides.

8. The method of claim 6, wherein said polypeptides are tumor antigens.

9. The method of claim 1, wherein said ligands are in a cell lysate.

10. A method for identifying an antibody having selective affinity for a tumor antigen, comprising the steps of:

a) selectively immobilizing a diverse population of antibodies to a solid support;

b) simultaneously contacting said diverse population immobilized on said solid support with two or more tumor antigens; and

c) determining at least one antibody which selectively binds to one or more of said tumor antigens.

11. The method of claim 10, wherein said population of antibodies are human antibodies or functional fragments thereof.

12. The method of claim 10, wherein said population of antibodies is produced in an expression library.

13. An isolated binding polypeptide selective for a tumor antigen, said binding polypeptide an antibody fragment selected from the group of antibody fragments consisting of F3, F13, F14, F15, F19, F21, F22, F23, F26, F30, F31, F32, F33, F34, F35, F36, F37, F38, F40, F41, F42, F46, F49, F50, F52, F54, F55, F58, F63, F66, F67, F68, F69, F70, F72, F74, F76, F78, F79, F80, F81, F84, F85, F86, F93, F99, F104, F111, F112, F118, F126, F129, F130, F132, F133, F134, F135, F136, F138, F151, F158,

F160, F174, F176, F177, F184, F186, F191, F197, F200, F202, F203, F207, F208, F212, F214, F217, F224, F231, F236, F238, TA50 and TA73.

14. An isolated binding polypeptide selective for a tumor antigen, said binding polypeptide an antibody fragment selected from the group of antibody fragments consisting of F3, F14, F15, F19, F21, F22, F23, F26, F133, TA50 and TA73.

15. The antibody fragment of claim 14, comprising substantially an amino acid sequence selected from the group consisting of the amino acid sequences referenced as SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, and SEQ ID NO:136.

16. An isolated nucleic acid molecule encoding an antibody fragment, comprising a nucleotide sequence encoding substantially an amino acid sequence selected

from the group consisting of the amino acid sequences referenced as SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, and SEQ ID NO:136.

17. The isolated nucleic acid molecule of claim 16, comprising a nucleotide sequence selected from the group consisting of the nucleotide sequences referenced as SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:79, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:97, SEQ

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18. A Complementarity Determining Region (CDR) or functional fragment thereof of an antibody selective for a tumor antigen, said CDR derived from an antibody fragment selected from the group consisting of F3, F13, F14, F15, F19, F21, F22, F23, F26, F30, F31, F32, F33, F34, F35, F36, F37, F38, F40, F41, F42, F46, F49, F50, F52, F54, F55, F58, F63, F66, F67, F68, F69, F70, F72, F74, F76, F78, F79, F80, F81, F84, F85, F86, F93, F99, F104, F111, F112, F118, F126, F129, F130, F132, F133, F134, F135, F136, F138, F151, F158, F160, F174, F176, F177, F184, F186, F191, F197, F200, F202, F203, F207, F208, F212, F214, F217, F224, F231, F236, F238, TA50 and TA73.

19. A Complementarity Determining Region (CDR) or functional fragment thereof of an antibody selective for a tumor antigen, said CDR derived from an antibody fragment selected from the group consisting of F3, F14, F15, F19, F21, F22, F23, F26, F133, TA50 and TA73.

20. The CDR of claim 19, comprising substantially an amino acid sequence selected from the group consisting of the amino acid sequences referenced as SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52,

SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, and SEQ ID NO:136.

21. An isolated nucleic acid molecule encoding a CDR, comprising a nucleotide sequence encoding substantially an amino acid sequence selected from the group consisting of the amino acid sequences referenced as SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, and SEQ ID NO:136.